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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Use of a Known Chemical Compound for the Production of a Pharmaceutical Composition for Topical Application

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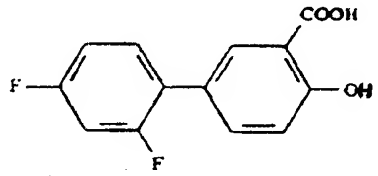


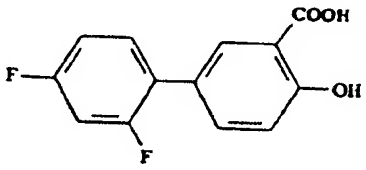
(I)

(57) Abstract

The compound diflunisal (5-(2,4-difluorophenyl)-salicylic acid) of formula (I) is used for the production of a pharmaceutical composition for treatment of inflammatory and/or autoimmune diseases, such as psoriasis, Crohn's disease and uveitis. Preferably compositions, such as cremes and ointments, for local use on skin surfaces, eye agents, compositions for local treatment of the intestinal canal, vaginal agents, compositions for local use in the oral cavity and compositions for inhalation are produced.

Use of a known chemical compound for the production of a pharmaceutical composition for topical application

The present invention concerns the use of the compound diflunisal (5-(2,4-difluorophenyl)-salicylic acid) of the formula:



for the production of a pharmaceutical composition for topical treatment of inflammatory and/or autoimmune diseases, such as psoriasis, Crohn's disease and uveitis.

An example of these diseases is psoriasis which is a cronic skin disease of unknown etiology. The indidence is about 2-3% in most western countries. The disease is hereditary, presumably polymerically conditioned, with irregularly occurring manifestations that may be caused mechanically, but probably also by other influences, infections, psychic strain, etc. The onset of the disease is usually at the age of 20-30. It manifests itself as regular, slightly infiltrated, hyperemic patches which are covered by stearin-like scales consisting of many layers. The disease is localized to the epidermis, and it is characterized by increased cell turnover. The normal cell turnover, which means the time it takes for a recently formed cell to get from the basal cell layer to the horny layer at the surface of the skin, is usually about 4 weeks, but in case of psoriasis it just takes 2-3 days.

According to the clinical nature of the disease a distinction is made between a number of different clinical forms, all of which are comprised by the designation "psoriasis" in the present context.

A plurality of modes of treatment have been employed in the course of time with a view to keeping the disease under control (1): Thus, drugs are used for topical application, such as corticosteroids, calcipotriol, anthralin (dithranol) and coal tar. In severe cases systemic treatment with drugs is used, such as methotrexate or aromatic retinoids, and phototherapy alone or in combination with psoralens. Combinations of these systemic and topical modes of treatment have been in general use in recent years.

The more effective treatments usually involve a high risk of serious side effects. Topically applied corticosteroids are moreover rendered more or less ineffective after a relatively short time. Anthralin is difficult to administer for the patient owing to discoloration and a considerable risk of inducing serious irritations, although these drawbacks have been mitigated to some extent after the introduction of the so-called minute therapy, comprising applying the drug to the skin for just 10-30 minutes. Topical treatment with tar is not used very much in Europe, in contrast to the widespread use in the USA where the treatment is considered rather effective when the tar application is followed by UVB iradiation (Goeckermann's treatment). However, the treatment with tar is inexpedient, because the tar composition is greasy and malodorous.

Systemic use of methotrexate is probably one of the most effective methods for the treatment of psoriasis in patients who are not in the fertile age, but it involves a potential risk of liver side effects, and it is therefore

to be supervised carefully.

Retinoids may be used, but serious side effects in this connection have been reported. These comprise induction of liver side effects and in some cases articular deformations. Etretinate (Tigason®), which is so far the only aromatic retinoid introduced for the treatment of psoriasis, is moreover teratogenic, and since its half life in the body is long, it is recommended that pregnancy during the treatment or within the first 12 months after the cessation of the treatment should be interrupted by abortion.

The D vitamin analog compound calcipotriol is another applicable agent for the treatment of psoriasis, because the compound inhibits the proliferation of the epidermal cells (2). However, it is marketed as an ointment, which may be inconvenient to use for the patient, and the medicament is not recommended for use on pregnant women owing to the still limited experience.

The T cell inhibiting substance cyclosporin A has a clear effect on inflammatory diseases, such as e.g. psoriasis (3). However, the substance has a number of adverse systemic side effects and is moreover difficult to use locally.

Thus, there is still a need for new modes of treatment and medicaments against psoriasis, just as there is need for new compositions for convenient topical treatment of other local inflammatory diseases, such as e.g. colitis ulcerosa, Crohn's disease, uveitis, contact dermatitis and cutaneous herpes simplex.

In case of these diseases as well as psoriasis it is believed that immunological mechanisms are involved in the pathogenesis, where particularly T lymphocytes play a part

(4,5,6,7). Such diseases are moreover characterized by a generally increased cell proliferation of e.g. inflammatory cells, including T cells, and possibly of epidermal cells.

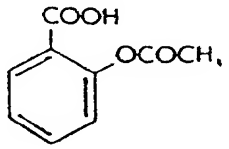
Therefore, a topical drug against psoriasis and other inflammatory and/or autoimmune diseases must satisfy the following requirements:

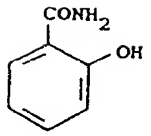
- It must exert an inhibitory effect on the cell proliferation (also on T lymphocytes) without simultaneously being decidedly cell toxic; cf. the effect of e.g. conventional cytostatics and cyclosporin A;

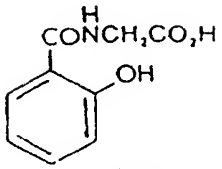
- it must be absorbable to a considerably degree from external and internal body surfaces for local activity, and

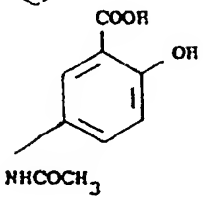
- it must not involve side effects in the form of local irritation, discoloration, etc.

It has surprisingly been found that the compound 5-(2,4-difluorophenyl)-salicylic acid (diflunisal) of the formula shown above has the above-mentioned desirable combination of properties. The compound has thus been found to have an extremely potent effect with respect to inhibition of cell proliferation, also on T cells, whereas structurally related compounds, such as

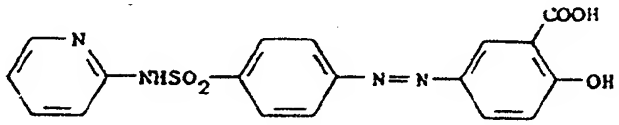
acetylsalicylic acid 

salicylamide 

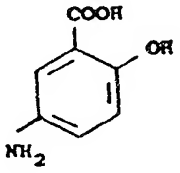
salicyl glycine  and

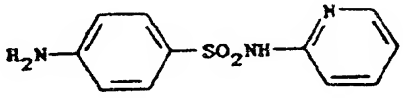
5-amidosalicylic acid 

have been found to have no activity in therapeutically relevant concentrations. On the other hand, a certain inhibitory effect on T cell proliferation can be observed with sulfasalazine (SASP):

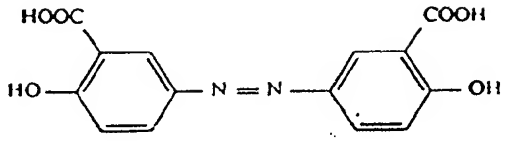


However, this property is observed only to a very limited degree for the metabolites of sulfasalazine:

5-aminosalicylic acid (5-ASA)  and

sulfapyridine 

and to some extent in the azo compound

olsalazine 

In addition to the relatively modest activity of sulfasalazine and olsalazine with respect to inhibition of cell proliferation, these compounds moreover give rise to inconvenience in the form of discoloration and discomfort when applied to the skin, and they will therefore not be expedient as drugs.

However, diflunisal has the necessary effect with respect to inhibition of cell proliferation of disease-relevant cells, and since the compound has moreover been found to be absorbed surprisingly easily through the skin without giving rise to inconvenient side effects, it is extremely suitable for the production of topical drugs against psoriasis and other inflammatory diseases. In addition to being useful for application on skin, diflunisal can be formulated as eye agents for the treatment of uveitis and as agents intended for local treatment in the intestinal canal, as well as optionally as agents that can be used on other body surfaces.

Diflunisal is a well-known medicament of analgesic and antiinflammatory activity (8). In Denmark the substance is known from the analgesic compositions Diflonid® and Donobid®, both of which are in tablet form. The substance has not yet been marketed in the form of compositions for topical administration, although other modes of administration for diflunisal than the oral one have been studied. The article (9) mentions a rectal dose form of diflunisal,

in which the base material is fatty compounds and polyethylene glycols, but it is stated that the rectal absorption is poor with respect to oral administration because of the poor solubility of diflunisal. According to (10) compositions for e.g. vaginal and rectal administration of diflunisal can be prepared with a view to treatment of inflammatory diseases, but it is necessary here to use hydrogenated phospholipids and a fatty base material to increase the bioavailablity of diflunisal which has poor absorbability through mucosal membranes. It has also been attempted to increase the penetration of diflunisal through the skin by using more readily soluble salts of diflunisal instead of free diflunisal, e.g. the diethylammonium salt (11). Finally, the compound has been used for topical treatment of acne in combination preparations, which moreover contain an antimicrobial agent in the form of a lipophilic 1-substituted imidazole; see reference (12).

Reference (13) describes pharmaceutical compositions for the treatment of i.a. psoriasis, preferably for topical application. These compositions comprise the substances 4-aminosalicylic acid (4-ASA), 5-aminosalicylic acid (5-ASA) or functional derivatives thereof. Diflunisal is not comprised by the patent claims of this reference. The clinical results with respect to the action of 5-ASA on psoriasis are still uncertain, and 5-ASA moreover gives rise to discoloration of the skin after oxidation with the oxygen of the air. Although the compound has a well-documented useful activity against Crohn's disease and colitis ulcerosa, the mode of action has still not been fully explained.

According to reference (14) diflunisal can be used perorally against psoriasis. The mode of action is stated to be based on inhibition of lipoxygenase, interfering with

the biotransformation of arachidonic acid to LTB_4 (leukotriene B_4 and 5-HETE (5-hydroxyeicosa[5.8.10.14]tetraenoate). This is said to counter the psoriasis attack which gives high arachidonic acid and 5-HETE levels. However, the reference contains no documentation of the actual achievement of a favourable activity against psoriasis, and if the oral administration of diflunisal is to give the asserted effect, it is necessary to administer extremely large doses (of the order of 200-1200 mg every 6th or 12th hour).

According to the present invention diflunisal can be formulated for a plurality of different modes of administration in connection with the present use of diflunisal for the production of topical drugs against inflammatory and/or autoimmune diseases.

As stated in the following table 1, which is copied from reference (15), drug forms for topical application may occur in various states (solutions, emulsions, suspensions) based on various vehicles. As a drug form containing diflunisal irrespective of state and vehicle, the use of the following ones is preferably contemplated: cremes (including foam), gels, liniments (including lotions), pastes, powders, ointments, shampoo, sticks, suppositories, enemas, controlled release formulations, vaginal agents, aerosols for inhalation, oral agents for local use in the oral cavity, eye drops and eye ointments, drug forms for topical application may occur in various states, as illustrated in the table.

TABLE 1

Drugs for topical application. Taxonomy according to state and drug forms.

State	Vehicle	Drug form
Liquid	Solution (hydrophilic or hydrophobic)	Liniment, Shampoo
	Suspension (hydrophilic or hydrophobic)	Liniment
	Emulsion (o/w,w/o)	Liniment
Semi-solid to semi-liquid single phase system	Hydrophobic gel water-emulsifying gel	Ointment
	Hydrophilic gel	Ointment, gel
Semi-solid to semi-liquid double phase system	w/o emulsion o/w emulsion	Creme
	Suspension	Ointment, Paste
Solid	Powdered mixture	Powder

The activity of various NSAID (NSAID = Non Steroid Anti Inflammatory Drug) including diflunisal, on the cell proliferation of a number of cell types incorporated in inflammatory and immunological mechanisms is shown below. Further, data for formulation and application of diflunisal to the skin are presented.

Methods

The following methods are used for partly studying the activity of diflunisal in vitro and partly studying the suitability for formulation as a drug:

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IN VITRO EXPERIMENTS

1. Antigen-specific T cell proliferation

Inbred mice of either the Balb/c type or the Blab/k type were used in all the experiments. The mice were immunized with a single injection in hind paws and tail stub with 0.1 ml of a water-in-oil emulsion containing equal parts of phosphate buffered salt water (PBS) and complete Freund's adjuvant containing Mycobacterium butyricum (Difco) and in some experiments 1 mg/ml antigen in the form of a peptide (MP7 having the sequence PELFEALQKLFKHAY) (16). Ten days later the mice were killed, and lymph glands in the pelvis and the groin were removed. Single cell suspensions of these were produced by passage through a steel net. Antigen (PPD (100 µg/ml) or MP7 (30 µg/ml)) as well as the various NSAID compositions were then admixed with microtiter plate cultures of the lymph gland cells containing 5×10^5 cells per well. The cells were cultured in RPMI containing penicillin, streptomycin, 2-mercapto ethanol, glutamine, sodium pyruvate and 0.5% syngenic fresh-drawn mouse serum. After 72 hours 1 µCi ^{3}H-thymidine was added to each well, and the cells were harvested after 90 hours. The ^{3}H-thymidine incorporation, as an expression of the T cell poliferation, was then determined by liquid scintillation count.

2. LPS and Con A stimulation of B and T lymphocyte proliferation, respectively

Mouse spleens from either Balb/c or Balb/k mice were removed, and single cell suspensions were produced as above. Erythocytes were lysed with hypotonic salt water and the spleen cells were washed twice in RPMI. The cells were then cultured in the same media as stated above in round bottom microtiter plates for 22 hours together with either

lipopolysaccharide (LPS) (100 µg/ml) or concanavalin A (Con A) (1 µg/ml) and dilutions of NSAID compositions as well as 1 µCi ^{3}H-thymidine. The cells were finally harvested and were then analyzed by liquid scintillation counts as described above.

3. Inhibition of proliferation of WeHi and X63 cells

WeHi and X63 cells, respectively, were cultured in RPMI with the same additions as above in microtiter plates with 5×10^{4} cells per well. However, mouse serum was replaced by 10% foetal calf serum in the medium. The cells were cultured for 4 hours together with NSAID dilutions and 1 µCi ^{3}H-thymidine per well, and they were then harvested and counted as described above.

All the NSAID compositions were examined in concentrations of from 15.6 to 1000 µM, and all the determinations were performed in triplicate, just as all the experiments were reproduced at least three times.

The percentage inhibition of LPS, Con A and antigen stimulated cells was calculated according to the following formula:

$$\% \text{ inhibition} = 100 - \frac{CPM_{\text{NSAID treated cells}} - CPM_{\text{non-stimulated cells}}}{CPM_{\text{NSAID non-treated cells}} - CPM_{\text{non-stimulated cells}}} * 100$$

The inhibition of WeHi and X63 cells (which do not have to be stimulated) was calculated as follows:

$$\% \text{ inhibition} = 100 - \frac{CPM_{\text{NSAID treated cells}}}{CPM_{\text{NSAID non-treated cells}}} * 100$$

Study of the absorption of diflunisal through the skin

The absorption of diflunisal through the skin was measured indirectly by secretion of the substance in the urine.

To design a suitable HPLC analysis for determination of free diflunisal and the glucuronidized derivatives thereof, respectively, an initial experiment was performed. 500 mg of diflunisal were administered orally, and a urine sample was collected subsequently. The urine sample was treated with β-glucuronidase to obtain cleavage of both phenol and acyl glucuronides to free diflunisal. The total amount of diflunisal in the urine could then be determined quantitatively by means of standards of diflunisal chromatographed under similar circumstances.

Two series of experiments were performed. One comprised applying to an individual who does not suffer from psoriasis or other skin diseases, a solution of diflunisal in propylene glycol (25 mg/ml). 1 ml of solution was applied to each arm in the morning and in the evening for 3 days. The total daily dose was 50 mg of diflunisal. Urine samples were collected over four subsequent days.

In the second series of experiments a non-aqueous foam formulation was applied to the same test person as described in example 1, containing diflunisal dissolved in propylene glycol (24 mg/ml). 2.5 ml were applied to each arm in the morning and in the evening for six days. The total applied daily dose was 240 mg of diflunisal. Urine samples were collected during the entire period and for another two days. The content of diflunisal in the various day diureses appears from table 3.

Results and discussion

In vitro activity on a plurality of disease-relevant cell types.

Sulfasalazine (SASP) and 5-aminosalicylic acid (5-ASA) have been used very successfully in the treatment of Crohn's disease and colitis ulcerosa. As appears from figs. 1a and 1b, SASP has a direct inhibitory activity on both antigen-specific as well as Concanavalin A (Con A) stimulated murine T cell proliferation. However, this property is only seen to a limited degree for the metabolites of SASP (5-ASA and sulfapyridine (SP)). An activity of olsalazine (OS), consisting of an azo compound between two 5-ASA molecules, is likewise seen.

Similar (but indirect) results have previously been reported for SASP, SP and 5-ASA, it being found that SASP was capable of inhibiting antibody production from murine spleen cells. It was believed that this was an indirect consequence of a simultaneously reduced production of interleukin-2, which is produced by T cells (17).

However, it has been found that this inhibiting activity is not specific for T cells, but, on the contrary, the proliferation of other cells is inhibited to the same extent. Figs. 2a and 2b show partly the effect on Con A stimulated T lymphocytes and partly the effect on LPS stimulated B lymphocytes from mouse spleens. There is no difference in the inhibition of the two cell types, in contrast to the effect of the T cell specific substance cyclosporin A (CSP).

Further, pronounced inhibition of the proliferation of two rapidly growing tumor cells, X63 and WeHi, is demonstrated, said cells being a B cell and a monocyte/macro-

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phage cell line, respectively. The last-mentioned cell type plays an important part in inflammatory processes. SASP inhibits 50% of the cell division over a period of 4 hours in concentrations from 700 to 1000 µM. The effect of SP and 5-ASA on these cells is even less pronounced (fig. 3). All experiments were performed with substance concentrations of the same order as the plasma concentration after a normal therapeutic peroral administration.

Using the same in vitro experiments a plurality of other derivatives were then examined with a view to finding more potent substances.

As will be seen from figs. 4a and 4b, salicylic acids, derivatised with e.g. an acetyl group on the OH group (acetylsalicylic acid), or in which the carboxylic acid group has been converted to an amide (salicylamide and salicyl glycine), have no noticeable effect on the cell proliferation, like 5-ASA.

Studies of salicylic acid derivatives with substitutions in the 5-position (figs. 5a-d) show that 5-phenylsalicylic acid (PS) (18), diflunisal and SASP have an extremely good effect in relation to the unsubstituted compounds salicylic acid and 5-amidosalicylic acid which have practically no effect. This activity, which is the result of a substitution with a very hydrophobic phenyl compound in salicylic acid, can possibly be ascribed to a better ability of diflunisal and PS to penetrate cell membranes. Compared with the SASP dose response curve, the diflunisal and PS curve is much steeper, and a 100% inhibition in concentrations down to approx. 125 µM is shown. The same degree of inhibition was seen on all examined cell types. However, SASP and PS were somewhat less potent inhibitors of the proliferation of WeHi and X63 (figs. 5c and 5d).

The general antiinflammatory properties of the substances are largely believed to be due to inhibition of cyclooxygenase, but it has also been described that they are capable of interrupting the oxydative phosphorylation in the mitochondria (19), which leads to reduced ATP production and thereby inhibited cell function. However, for this effect to be achieved with salicylic acid, rather large doses are necessary. Various derivatives of salicylic acid have been studied in the experiments described below.

Owing to an assumption that the mechanism causing the observed effect of diflunisal might be ascribed to interruption of the oxidative phosphorylation in the mitochondria, two other NSAID compositions were moreover studied, viz. diclofenac and indomethacin, which are known to effectively cause such interruption. Figs. 6a and 6b show a comparison of the effect of diclofenac, indomethacin, PS and diflunisal on the proliferation of WeHi and X63 cells, respectively. As will be seen, these compounds are substantially equipotent with respect to the inhibiting effect on the cell proliferation. However, PS is somewhat less potent, and diclofenac and indomethacin, which are not salicylic acid derivatives, but acetic acid derivatives, and which are therefore not chemically analogous to diflunisal, appear to exhibit less effective absorption through the skin. This makes these substances less interesting in the present context. Furthermore, indomethacin and diclofenac are known to be locally irritating, and diclofenac moreover exhibits photosensibility, which makes the substances unuseful for local application.

Diflunisal is absorbed almost completely after oral administration of doses of 50-500 mg. The oral bioavailability is stated in the literature to be 100% based on recovery in the urine after 96 hours. Diflunisal is greatly bound to plasma proteins (20).

The elimination is concentration dependent and depends upon conjugation with glucuronic acid. About 80-95% of an oral dose is secreted in the urine 72-96 hours after administration, mainly as phenol (64%) and acyl glucuronides (20%).

The use of diflunisal for the treatment of psoriasis will be conditional upon the substance penetrating into the skin.

Penetration experiments were performed with two formulations: A solution of diflunisal in propylene glycol (25 mg/ml) and a foam formulation, as stated in example 1.

Application of diflunisal in propylene glycol was followed by collection of urine round the clock, which was analyzed on HPLC for diflunisal content. As appears from table 2, diflunisal can be absorbed very well through the skin and then be secreted in the urine.

TABLE 2

Day	Urine samples collected at	Urine volume (ml)	Urine conc. (µg/ml)	Total amount of diflunisal secreted per 24 hours (mg)
1	16:30	430	1.33	1.1
-	22:45	380	1.35	
2	06:45	610	1.75	10.0
-	11:00	410	5.79	
-	15:45	380	6.36	
-	19:00	650	2.17	
-	21:00	610	2.19	
-	23:00	620	2.21	
3	04:00	740	3.55	12.5
-	07:00	300	7.54	
-	21:00	550	13.8	
4	06:10	700	6.7	4.7

Diflunisal has thus been present in the epidermis, where the substance may give rise to inhibition of the proliferation of the epidermal cells as well as the pathogenic T cells.

After application of diflunisal in a foam formulation similar analyses of the content of diflunisal in the urine were performed. It appears from the results in table 3 that diflunisal is absorbed excellently through the skin here too. This experiment extended over a longer period

than the preceeding one, and after day 3 where a steady-state condition occurred, it can be seen that about 10% of the applied dose of diflunisal is secreted. The observed decline on day 5 is due to the fact that only a single dose was applied on this day.

TABLE 3

Day	Urine volume (ml)	Urine conc. (µg/ml)	Total amount of diflusnial secreted per 24 hours (mg)
1	2400	1.63	3.9
2	2700	6.11	16.5
3	3900	7.28	28.4
4	2400	10.70	25.7
5	3100	3.52	10.9
6	4000	6.56	26.2
7	3200	7.79	24.9
8	3250	2.18	7.1

In future formulations of diflunisal a number of factors must be taken into consideration:

When formulating cremes (including foam) it is possible i.a. to vary the lipophilicity and the viscosity of the base, whereby the drug release from the creme can be controlled. Likewise, it is possible to vary the foam quality by varying the content of isobutane. The formulation can also be varied with respect to penetration enhancing substances, so-called enhancers, e.g. ethanol and Azone®.

When formulating gels it is possible to formulate a hydrophobic as well as a hydrophilic gel. It applies to both of them that they will dry on the skin after application, thereby forming a firm brittle film. Hydrophilic gels have the advantage that they are not greasy. They can moreover be removed by ordinary washing, which is of importance in case of e.g. application on heary skin portions.

When formulating ointments a distinction is made between hydrophobic, hydrophilic and water emulsifying ointments. Hydrophobic ointments are ointments based on lipophilic vehicles, typically hydrocarbons, vegetable oils, semi-synthetic fats, waxes and alkyl polysiloxanes. Hydrophobic ointments absorb moisture from the skin only to a limited extent, and they therefore have an occlusive effect. They also have a good skin contact and have a softening effect on the horny layer after application for an extended period of time, which is desirable when the horny layer is thick. It applies to all types of ointments that stabilizing vehicles may be added, e.g. antioxidants, preservatives, and aromatic substances. Hydrophobic ointments also have a positive effect on scaly skin areas. Hydrophilic ointments are based on carriers which are miscible with water, most frequently polyethylene glycols. Water emulsifying ointments are based on lipophilic vehicles admixed with lanolin or other w/o emulsifying substances, e.g. sorbitan esters.

Concerning eye agents the aqueous formulations are the most common dosage form. Since diflunisal is sparingly soluble in water at a neutral pH, eye drops containing diflunisal will preferably be suspensions. The advantage of these is that the particles, after application, settle in the conjunctival sack of the eye in which they are dissolved slowly. This provides a depot effect. When using a drug form containing particulate diflunisal (suspension),

micronized diflunisal is preferably to be used, which means that the greater part of the particles is smaller than 5 µm and all the particles are smaller than 25 µM.

Diflunisal can also be formulated in a controlled release form for the treatment of inflammatory intestinal diseases, cf. reference (21). Formulation of enemas is also possible.

The invention will be illustrated more fully by the following formulation examples.

In the examples all percentages are percentages by weight.

EXAMPLE 1

Cremes

Diflunisal	0.01 - 10 %
Cetostearyl alcohol	0 - 15 %
Cetomacrogol 1000	0 - 3 %
Cetanol	0 - 15 %
Isopropyl myristate	0 - 15 %
Propylene glycol	10 - 50 %
White solid paraffin	0 - 15 %
Paraffin oil	0 - 15 %
Preservatives	q.s.
Ethanol	0 - 10 %
Water	0 - 60 %

Non-aqueous foam:

Diflunisal	0.01 - 10 %
Propylene glycol	86 - 96 %
Polawax	0.8 %
Brij 76	3.3 %
Preservative	q.s.
Isobutane	5.5 %
Nitrogen	to 6 bars

Aqueous foam:

Diflunisal	0.01 - 10 %
Polawax	0.5 - 5 %
Polysorbate 20	0.1 - 3 %
Propylene glycol	30 - 50 %
Softigen 767	10 - 30 %
Preservative	q.s.
Water	20 - 35 %
Isobutane	3 - 6 %
Nitrogen	to 5 - 7 bars

The produced foam bases are packed in aluminium cans which are closed with a valve, following which a dosing device is applied, which makes it possible to dispense doses from 1 to 5 ml. Such a valve with a dosing device is available e.g. from Lablabo, 5 rue Roger Salengro, 92120 Montrouge, France.

EXAMPLE 2

Gels

(a) Hydrophilic gels:

Diflunisal	0.01 - 10 %
"Carbomer" (acrylic acid polymer)	0 - 5 %
Sodium carboxymethylcellulose	0 - 5 %
Methylcellulose	0 - 5 %
Natural starches	0 - 25 %
Silicates	0 - 5 %
Bentonite	0 - 5 %
Preservatives	q.s.
Water	75 - 99 %
Glycerol	75 - 99 %
Propylene glycol	75 - 99 %

(b) Hydrophobic gels:

Diflunisal	0.01 - 10 %
Polyethylene	10 %
Paraffin oil	90 %

EXAMPLE 3

Liniments, including lotions

(a)	Diflunisal	0.01 - 10 %
	Propylene glycol	50 - 99 %
	Isopropyl myristate	0 - 10 %
	Sodium hydroxide 1 N	q.s.
	Hydrochloric acid 1 N	q.s.
	Glycerol	0 - 10 %

	(b)	Diflunisal	0.01 - 10 %
		"Carbomer"	0.5 - 2 %
		Cellulose rubber	0.5 %
		Polysorbate 80	0.1 %
		Glycerol 85%	0 - 5 %
		Propylene glycol	5 %
		Preservative	q.s.
		Water	84 - 94 %
	(c)	Diflunisal	0.01 - 10 %
		Glycerol 85%	0 - 10 %
		Propylene glycol	0 - 10 %
		Sorbitol	0 - 10 %
		Sodium chloride	0 - 5 %
		Ethanol	0 - 99 %
		Water	0 - 99 %
		Preservative	q.s.
	(d)	Diflunisal	0.01 - 10 %
		Cetomacrogol 1000	0.8 %
		Cetostearyl alcohol	3.2 %
		Clyceryl stearate	3 %
		Mineral oil	15 %
		Polysorbate 80	0.6 %
		Glycerol 85%	3 %
		Propylene glycol	5 %
		Preservative	q.s.
		Water	59 - 69 %

EXAMPLE 4

Pastes

Diflunisal	0.01 - 25 %
Vaseline	0 - 99 %
Lanolin	0 - 99 %
Mineral oil	0 - 10 %

EXAMPLE 5

Powders

Diflunisal	0.01 - 10 %
Sterilizable starch	90 - 99 %

EXAMPLE 6

Ointments

(a) Hydrophobic ointments:

Diflunisal	0.01 - 10 %
Paraffin	1 - 10 %
White wax	1 - 10 %
Cetostearyl alcohol	1 - 10 %
White vaseline	80 - 90 %

Diflunisal	0.01 - 10 %
Lanolin	1 - 10 %
Paraffin	1 - 10 %
Cetostearyl alcohol	1 - 10 %
White vaseline	80 - 90 %

(b) Water-emulsifying ointments:

Diflunisal	0.01 - 10 %
Anhydrous lanolin	20 %
White vaseline	70 - 80 %

(c) Hydrophilic ointments:

Diflunisal	0.01 - 10 %
Macrogol 300	65 %
Macrogol 4000	25 - 35 %

Diflunisal	0.01 - 10 %
Macrogol 400	60 %
Macrogol 3350	30 - 40 %

EXAMPLE 7

Shampoo

Diflunisal	0.01 - 10 %
Texapon SBN®	50 %
Sodium chloride	3 %
Preservative	q.s.
Water	37 - 47 %

The content may be increased to make the shampoo softer and thus more gentle to the skin.

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EXAMPLE 8

(a) Eye drops

Diflunisal	0.01 - 10 %
Preservative, e.g. benzalconium chloride	0.00 - 0.5 %
Methylcellulose	0 - 1 %
Polyvinyl alcohol	0 - 2 %
Sodium hydroxide to pH 7-9	
Sodium chloride	0 - 0.9 %
Tween	0 - 1 %
Polysorbate	0 - 1 %
Sterile water	up to 100%

(b) Eye ointments

Diflunisal	0.01 - 10 %
Vaselin	80 %
Paraffin oil	up to 100 %

Diflunisal	0.01 - 10 %
Cetanol	0 - 15 %
Lanolin	0 - 10 %
Paraffin oil	0 - 15 %
White vaseline	0 - 50 %
Sterile water	0 - 60 %

Description of figures

Fig. 1: Study of the ability of various SASP analog substances to inhibit the T cell activation. a. Inhibition of the antigen-specific T cell response to the synthetic peptide MP7 (PELFEALQKLFKHAY) with various concentrations of SASP, SP and 5-ASA. b. Inhibition of Con A stimulated T cells from spleens with various concentrations of SASP, SP, 5-ASA and Olsalazine.

Fig. 2: Study of whether various analog substances of SASP specifically inhibit T-cells. a. Inhibition of Con A stimulated T cells from spleens with various concentrations of SASP, SP, 5-ASA, Olsalazine and CSP. b. Inhibition of LPS stimulated B cells from spleens with the same substances. The unit on the top x-axes is the concentration range of CSP.

Fig. 3: Study of the effect of various SASP analog substances on two immunologically relevant tumor lines. a. Inhibition of the growth of WeHi cells (monocyte/macrophage line) of SASP, SP, 5-ASA and Olsalazine. b. Inhibition of the growth of X-63 cells (myeloma line) with the same substances.

Fig. 4: Study of the proliferation inhibition of T and B cells by addition of salicylic acid analog substances derivatised on the carboxylic acid group and the phenol group, respectively. a. Inhibition of Con A stimulated T cells from spleens with various concentrations of acetylsalicylic acid,

salicylamide, salicyl glycine and 5-ASA. b. Inhibition of LPS stimulated B cells with the same substances.

Fig. 5: Study of the proliferation inhibition of T and B cells by addition of salicylic acids derivatised in the 5-position. a. Inhibition of Con A stimulated T cells from spleens with various concentrations of 5-ASA, 5-amidosalicylic acid, 5-phenylsalicylic acid, diflunisal, salicylic acid and SASP. b. Inhibition of LPS stimulated B cells with the same substances. c. Inhibition of WeHi cells with the same substances. d. Inhibition of X-63 cells with the same substances.

Fig. 6: Study of the proliferation inhibition of tumor cells by addition of inhibitors of the oxidative phosphorylation. a. Inhibition of WeHi cells with diclofenac, indomethacin, diflunisal and phenylsalicylic acid. b. Inhibition of X-63 cells with the same substances.

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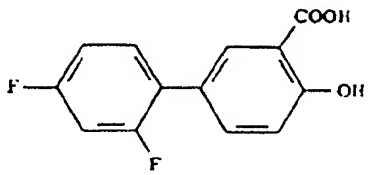
Patent Claims:

1. Use of diflunisal (5-(2,4-difluorophenyl)-salicylic acid) of the formula



for the production of a pharmaceutical composition for topical treatment of inflammatory and/or autoimmune diseases, such as psoriasis, Crohn's disease and uveitis, said composition containing 0.01-10% by weight of diflunisal in combination with ordinary, pharmaceutically acceptable vehicles and excipients.

2. Use according to claim 1, characterized in that compositions are produced for local use on skin surfaces in the form of cremes (including foam), gels, sticks, plasters, ointments, shampoo, liniments, powders or pastes.

3. Use according to claim 1, characterized in that compositions are produced for use as an eye agent in the form of eye drops or an eye ointment.

4. Use according to claim 1, characterized in that compositions are produced for local treatment of the intestinal canal in the form of controlled release

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formulations, suppositories or enemas.

5. Use according to claim 1, c h a r a c t e r i z e d in that compositions are produced in the form of cremes, gels, liniments, powders, pastes or vagitories for local treatment of inflammation in the vagina.

6. Use according to claim 1, c h a r a c t e r i z e d in that compositions are produced for local use in the oral cavity in the form of lozenges, mouth rinsing water or mouth ointments.

7. Use according to claim 1, c h a r a c t e r i z e d in a composition is produced in the form of an inhalation spray for local treatment of the respiratory passages.

8. A process for local treatment of psoriasis, c h a r a c t e r i z e d by applying to the patient a topical composition containing 0.01-10% by weight of diflunisal in combination with ordinary, pharmaceutically acceptable vehicles and excipients, on the affected part.

9. A process for local treatment of Crohn's disease, c h a r a c t e r i z e d by administering to the patient a composition for local treatment of the intestinal canal in the form of controlled release formulations, suppositories or enemas, said composition containing 0.01-10% by weight of diflunisal in combination with ordinary, pharmaceutically acceptable vehicles and excipients.

10. A process for local treatment of uveitis, c h a r a c t e r i z e d by administering to the patient a topical agent in the form of eye drops or an eye ointment

containing 0.01-10% by weight of diflunisal in combination with ordinary, pharmaceutically acceptable vehicles and excipients.

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fig. 1a

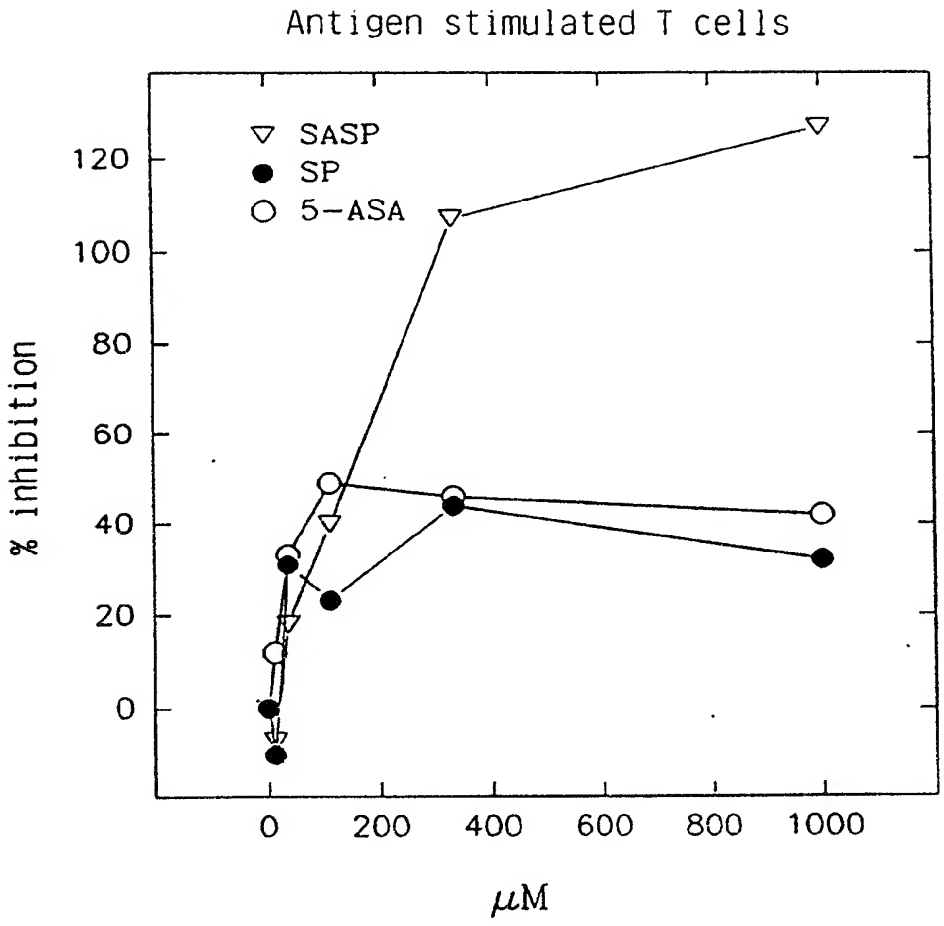


fig. 1b

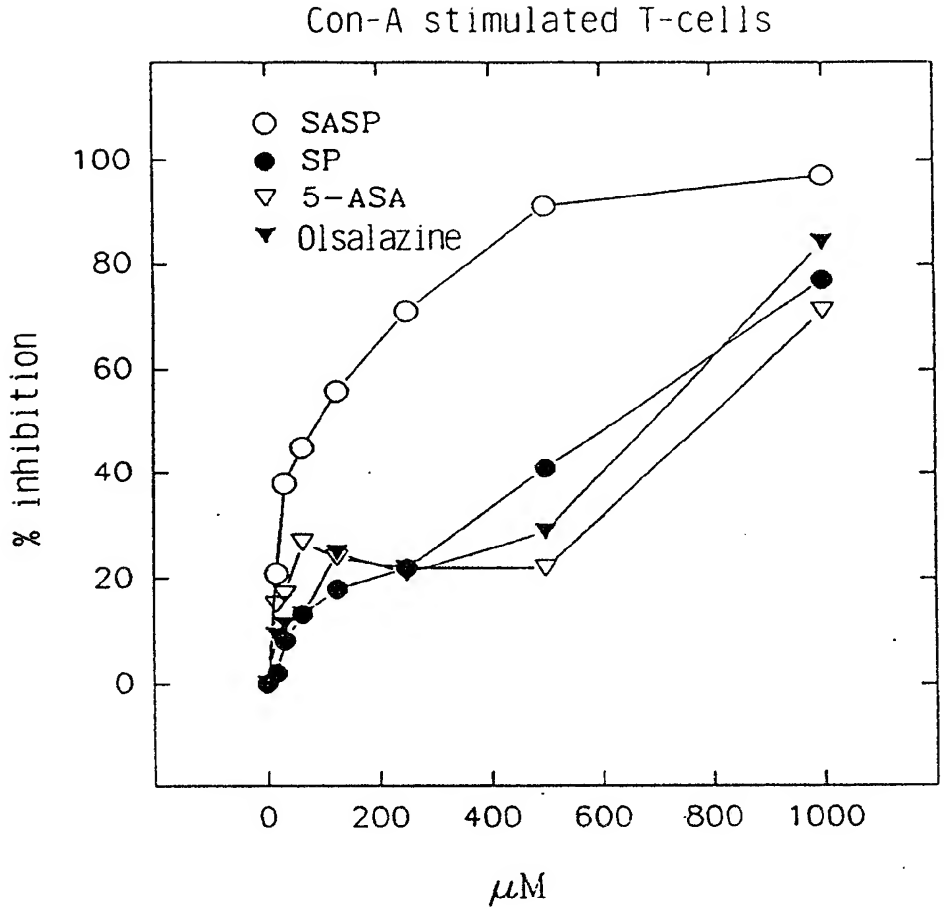

Con-A stimulated T-cells
SASP
SP
5-ASA
Olsalazine
% inhibition
100
80
60
40
20
0
0
200
400
600
800
1000
μM

fig. 2a

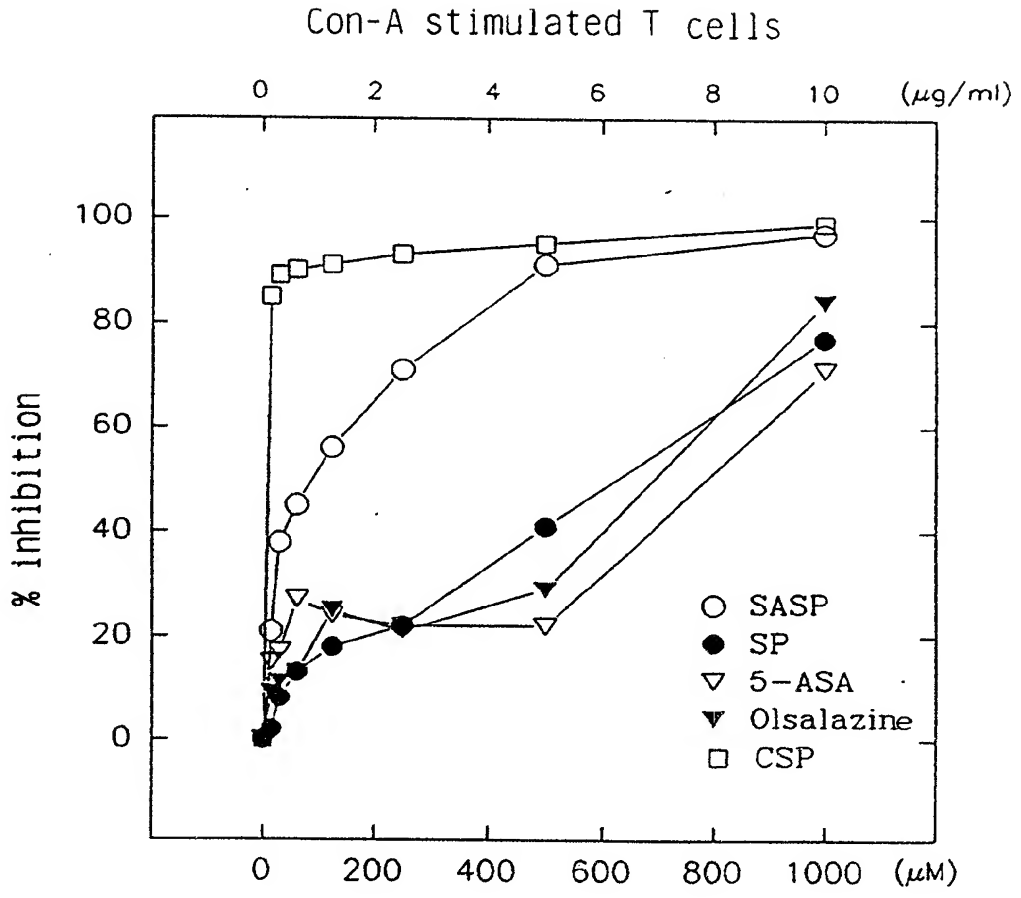

Con-A stimulated T cells
0
2
4
6
8
10
(μg/ml)
100
80
60
40
20
0
% inhibition
SASP
SP
5-ASA
Olsalazine
CSP
0
200
400
600
800
1000
(μM)

fig. 2b

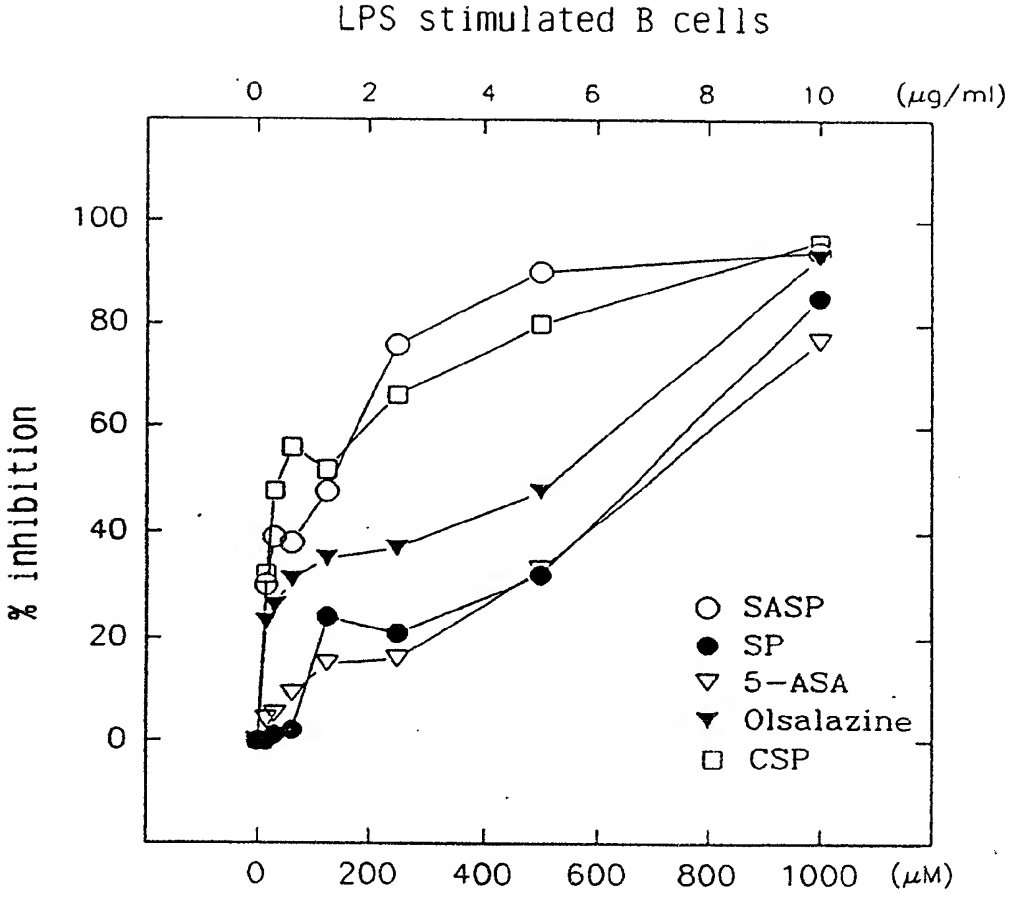

LPS stimulated B cells
0
2
4
6
8
10
(μg/ml)
100
80
60
40
20
0
% inhibition
SASP
SP
5-ASA
Olsalazine
CSP
0
200
400
600
800
1000
(μM)

fig. 3a

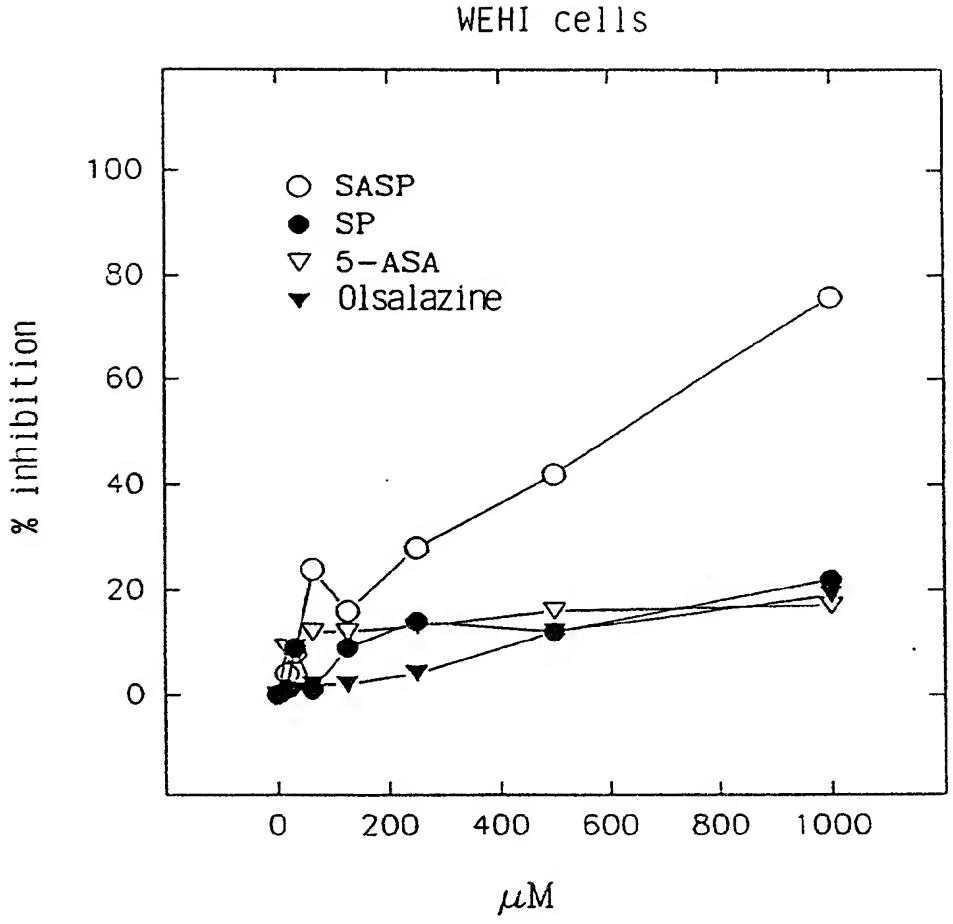

WEHI cells
% inhibition
100
80
60
40
20
0
SASP
SP
5-ASA
Olsalazine
0
200
400
600
800
1000
μM

fig. 3b

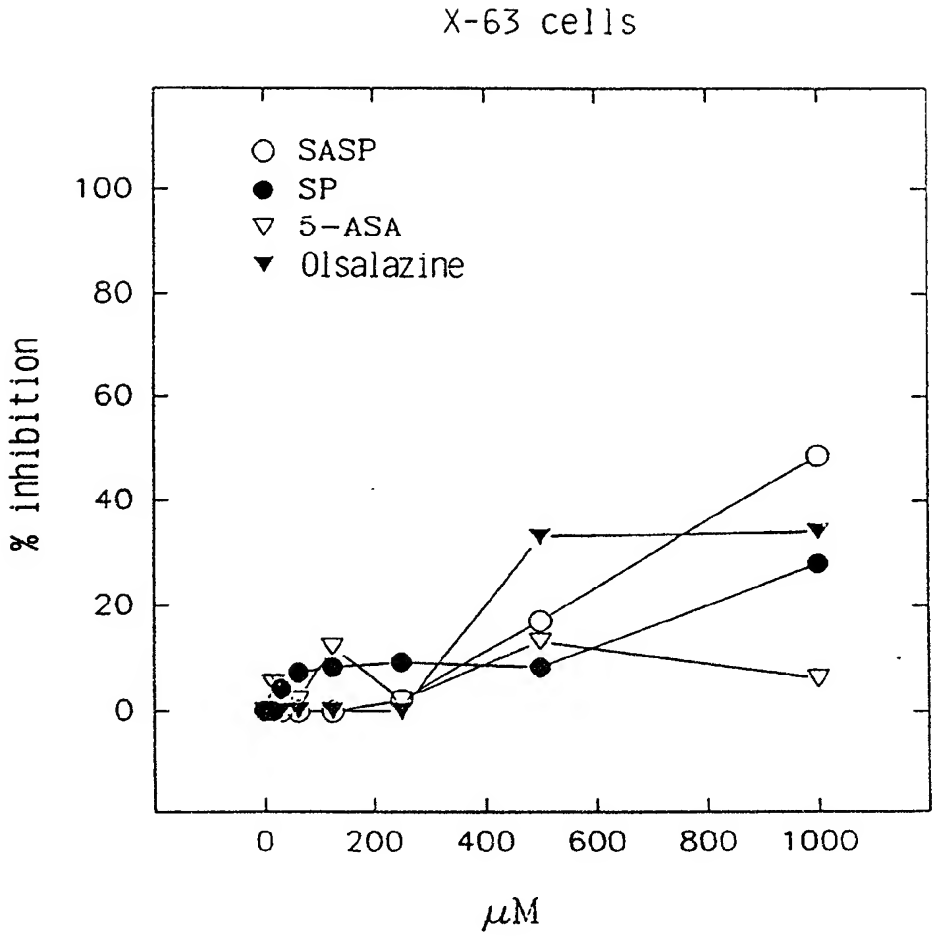

X-63 cells
SASP
SP
5-ASA
Olsalazine
% inhibition
100
80
60
40
20
0
0
200
400
600
800
1000
μM

fig. 4a

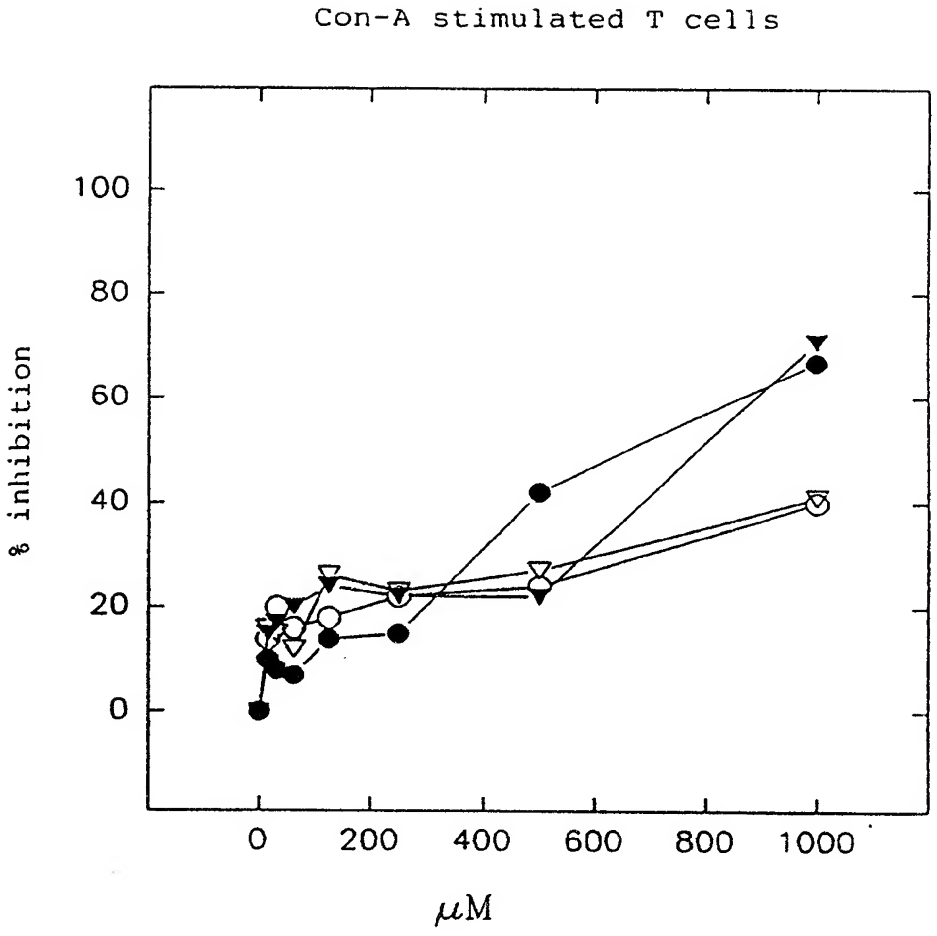

Con-A stimulated T cells
% inhibition
100
80
60
40
20
0
0
200
400
600
800
1000
μM
Acetylsalicylic acid
Salicylamide
Salicyl glycine
5-ASA

fig. 4b

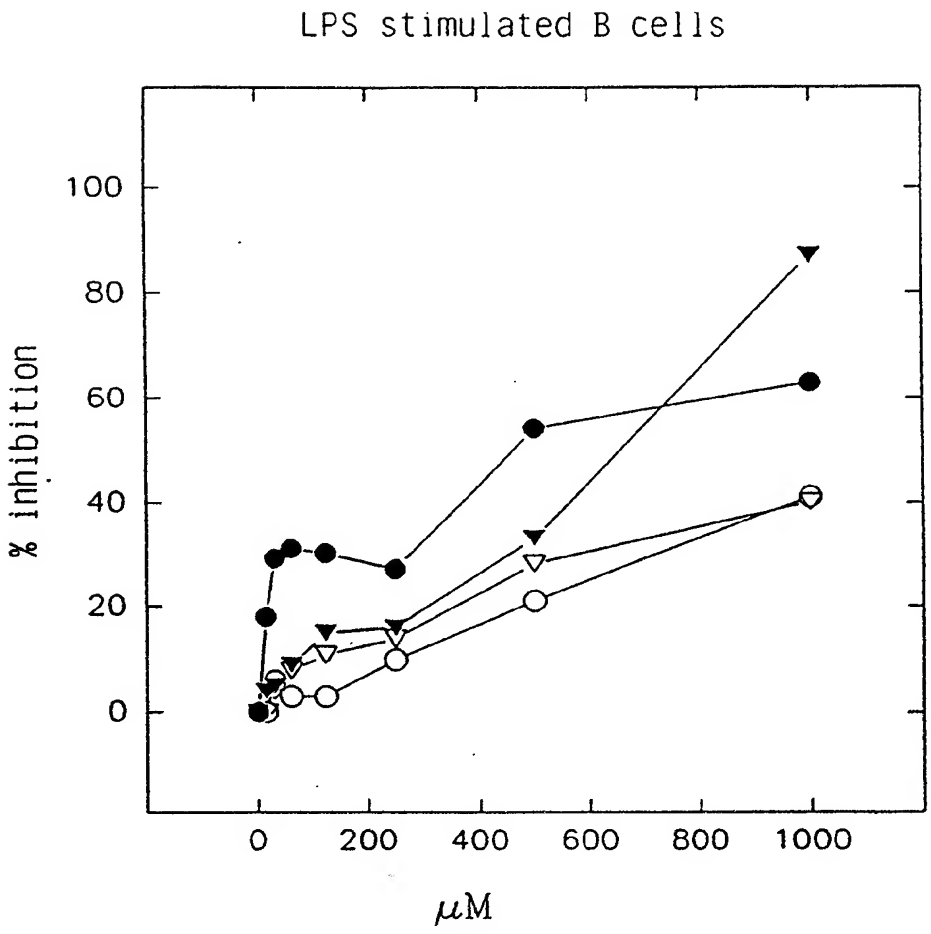

LPS stimulated B cells
% inhibition
100
80
60
40
20
0
0
200
400
600
800
1000
μM
Acetylsalicylic acid
Salicylamide
Salicyl glycine
5-ASA

fig. 5a

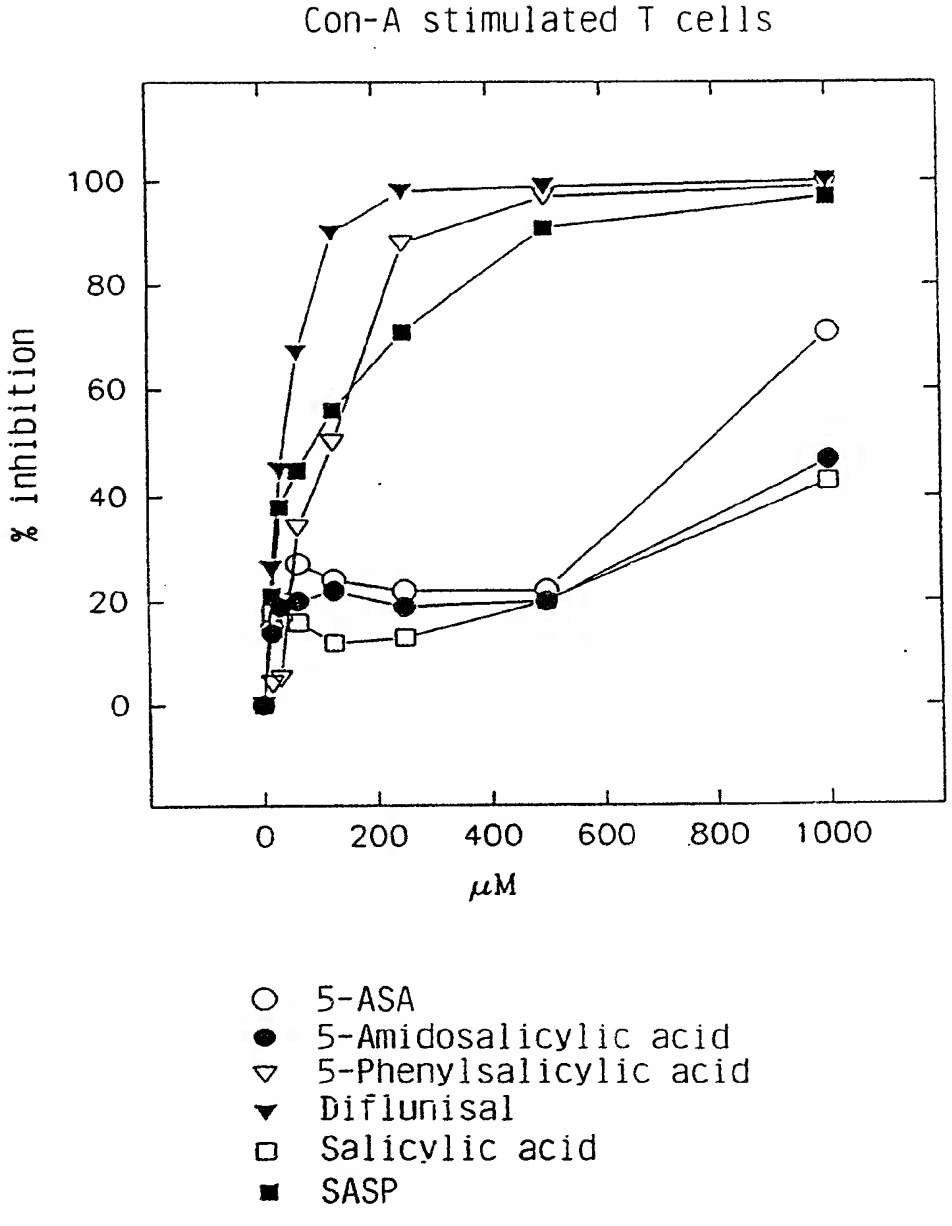

Con-A stimulated T cells
% inhibition
100
80
60
40
20
0
0
200
400
600
800
1000
μM
5-ASA
5-Amidosalicylic acid
5-Phenylsalicylic acid
Diflunisal
Salicylic acid
SASP

fig. 5b

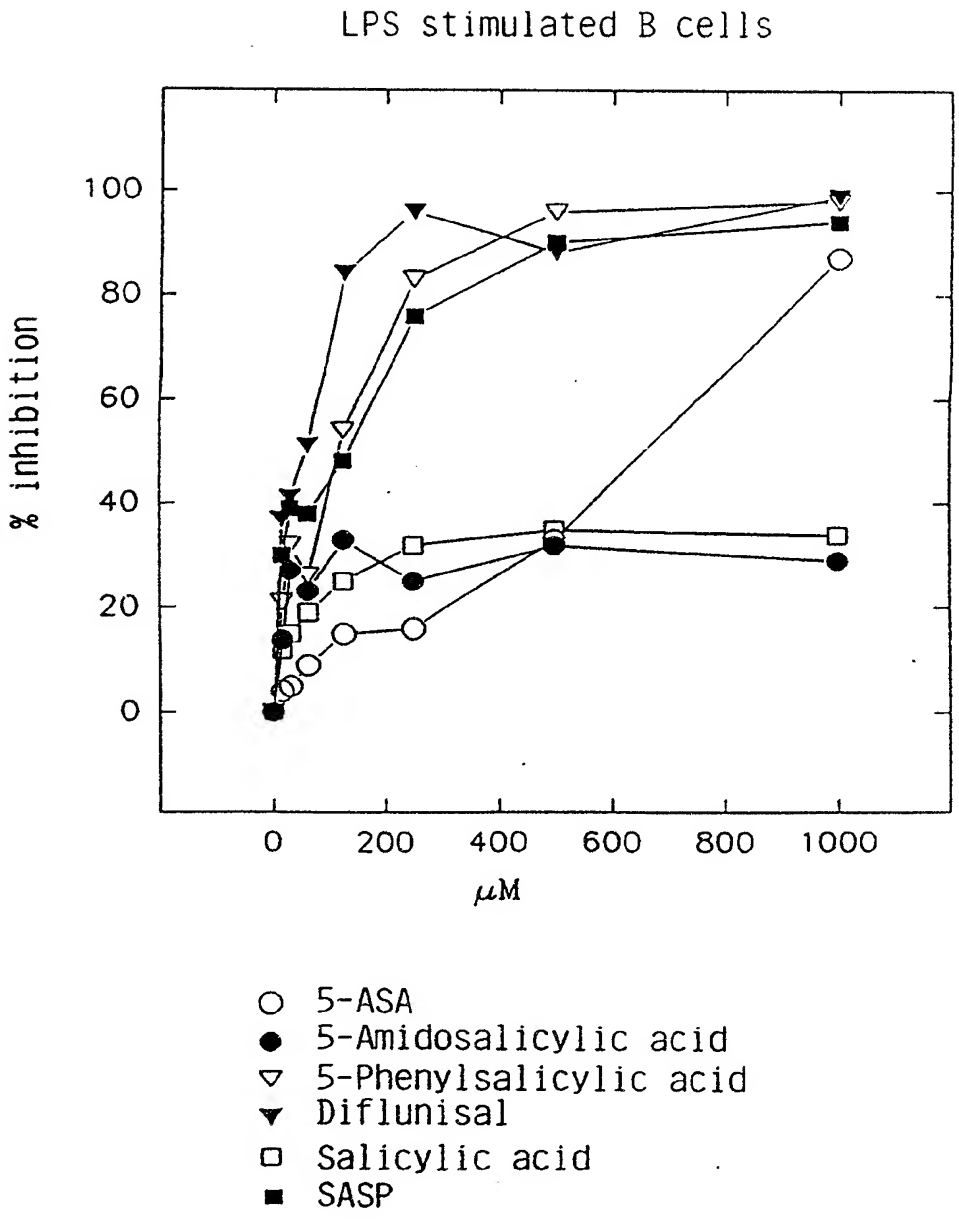
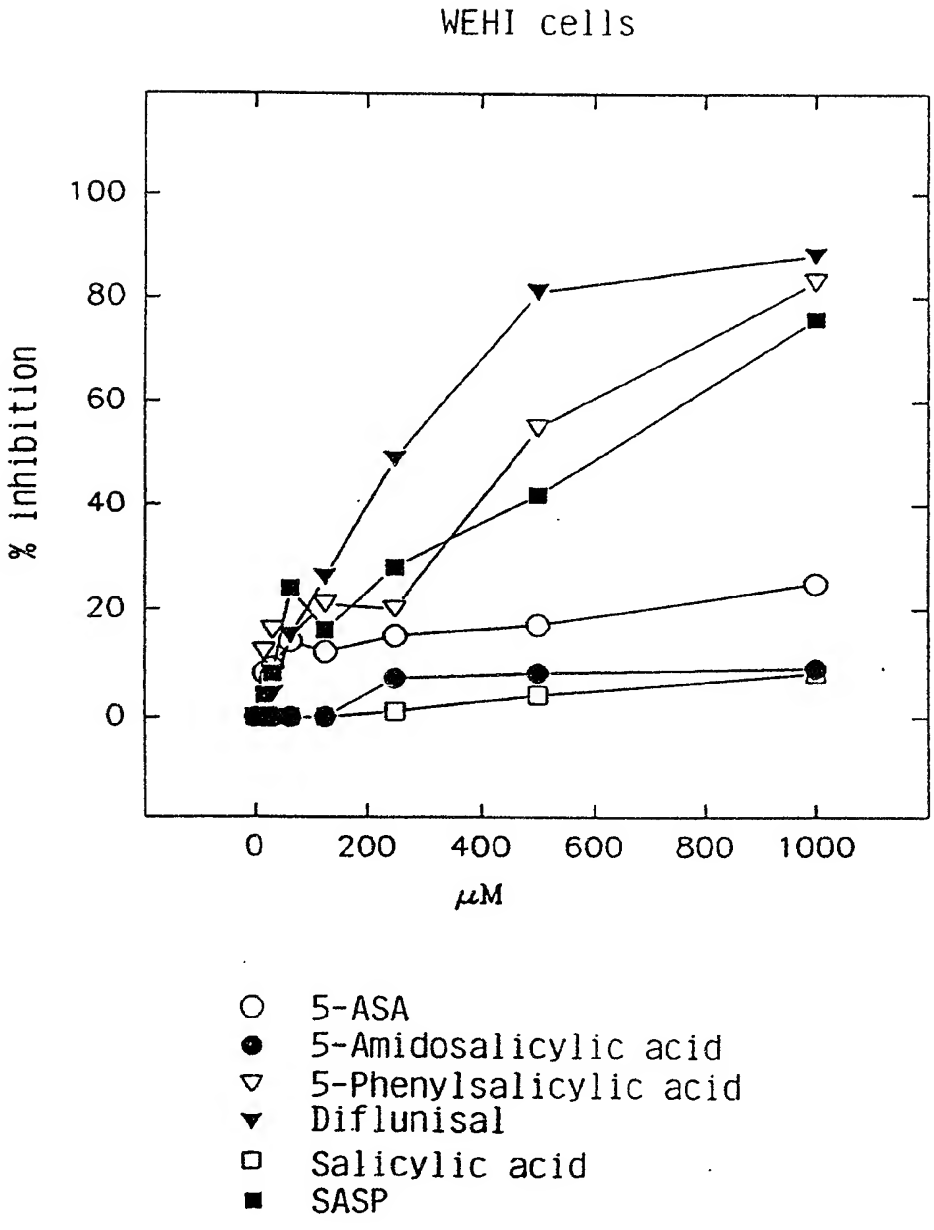

LPS stimulated B cells
% inhibition
100
80
60
40
20
0
0
200
400
600
800
1000
μM
5-ASA
5-Amidosalicylic acid
5-Phenylsalicylic acid
Diflunisal
Salicylic acid
SASP

fig. 5c


WEHI cells
% inhibition
100
80
60
40
20
0
0
200
400
600
800
1000
μM
5-ASA
5-Amidosalicylic acid
5-Phenylsalicylic acid
Diflunisal
Salicylic acid
SASP

flg. 5d

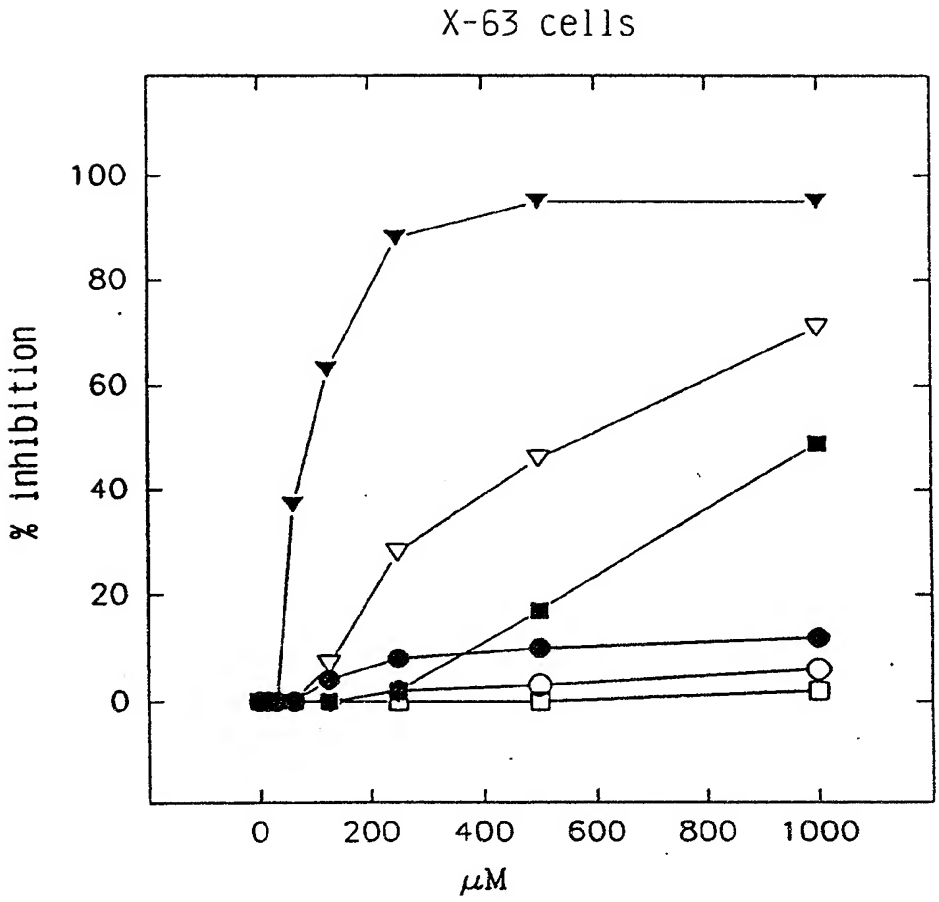

X-63 cells
% inhibition
100
80
60
40
20
0
0
200
400
600
800
1000
μM
5-ASA
5-Amidosalicylic acid
5-Phenylsalicylic acid
Diflunisal
Salicylic acid
SASP

fig. 6a

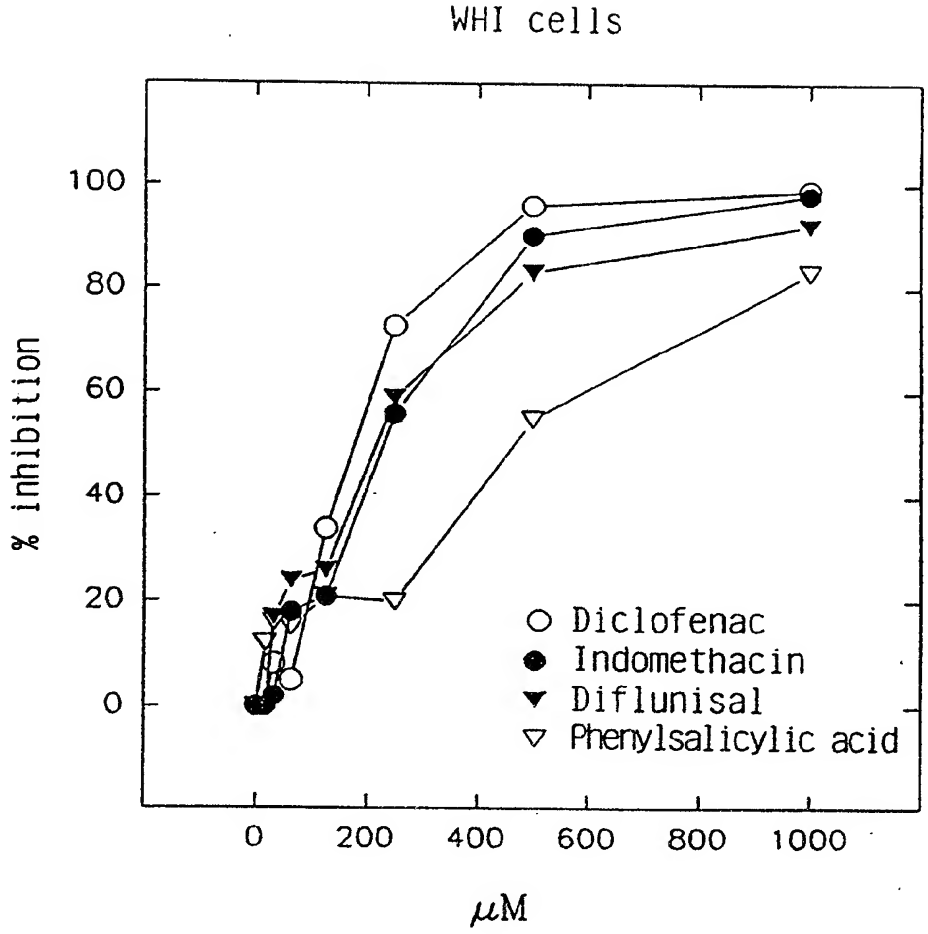
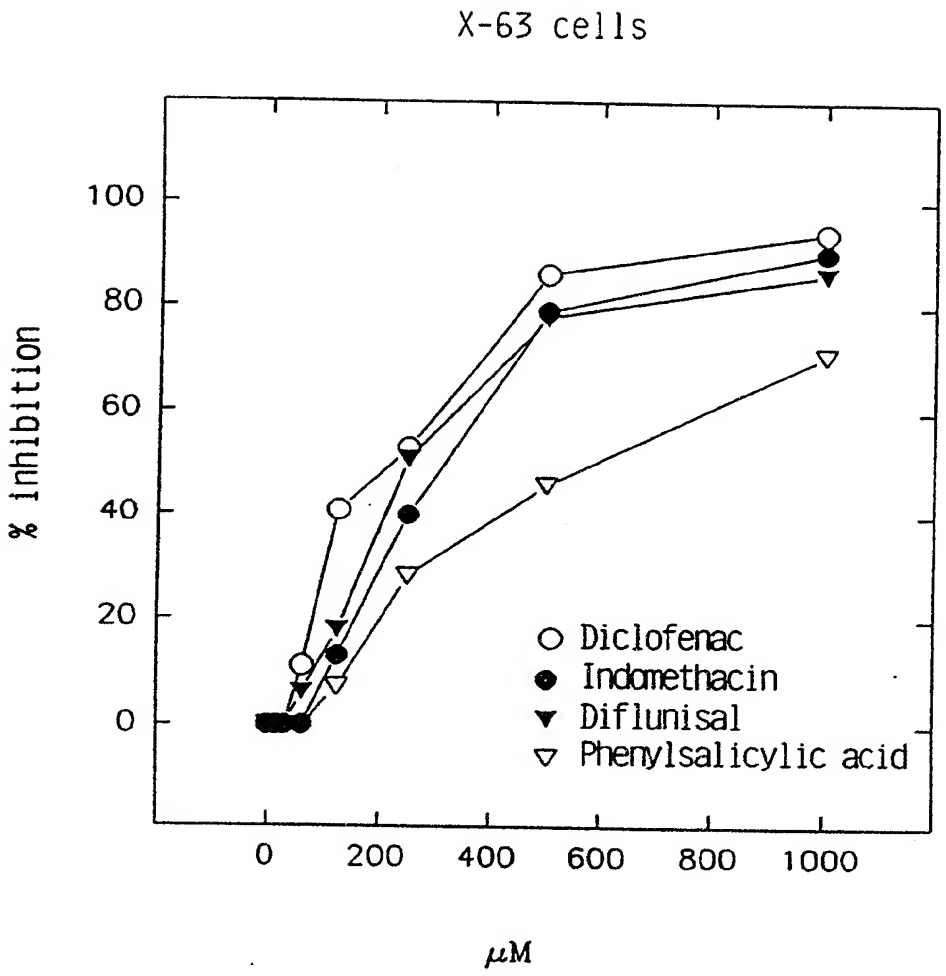

WHI cells
% inhibition
100
80
60
40
20
0
0
200
400
600
800
1000
μM
Diclofenac
Indomethacin
Diflunisal
Phenylsalicylic acid

fig. 6b


X-63 cells
% inhibition
100
80
60
40
20
0
0
200
400
600
800
1000
μM
Diclofenac
Indomethacin
Diflunisal
Phenylsalicylic acid